B' cont.

(iii) have a surface modifier adsorbed on the surface thereof; and

(b) the aggregates of spray-dried drug particles are less than or equal to about 100 microns in diameter.

Sub C2

23. (Twice Amended) A freeze-dried powder aerosol composition comprising aggregates of nanoparticulate drug particles, wherein:

(a) the aggregates of freeze-dried drug are less than or equal to about 100 microns in diameter;

(b) the nanoparticulate drug particles:

B2

(i) comprise a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml,

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(iii) have a surface modifier adsorbed on the surface thereof.

Sub C3

35. (Twice Amended) A dry powder nanoparticulate aerosol composition for use in a propellant-based pMDI comprising

(a) aggregates of a nanoparticulate poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml, wherein the aggregates are less than or equal to about 100 microns in diameter, and wherein the drug:

B3

(i) has a surface modifier adsorbed on the surface thereof, and [the drug]

(ii) has an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm[wherein the aggregates are less than or equal to about 100 microns in diameter], and

(b) a non-aqueous propellant.

40. (Twice Amended) A method of making a dry powder nanoparticulate drug composition comprising:

(a) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles and a surface modifier adsorbed on the surface thereof, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and

(ii) the drug particles have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm; and

(b) spray-drying the nanoparticulate dispersion to form a dry powder of aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns.

42. (Twice Amended) A method of making a dry powder nanoparticulate drug aerosol formulation comprising:

(a) milling under non-pressurized conditions [a poorly soluble crystalline drug and a surface modifier] in a non-aqueous medium having a high boiling point the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a nanoparticulate drug composition having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(b) evaporating the non-aqueous medium to obtain a dry powder of aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns.

43. (Twice Amended) A method of making a nanoparticulate drug aerosol formulation comprising:

(a) milling under pressurized conditions [a poorly soluble crystalline drug and a surface modifier] in a non-aqueous medium the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous dispersion medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a drug having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm; and

(b) evaporating the non-aqueous medium to obtain a dry powder of aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns.

B5 cont

44. (Twice Amended) A method of making a dry powder nanoparticulate drug composition comprising:

(a) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and wherein the drug particles have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(ii) a surface modifier adsorbed on the surface thereof[, wherein the drug particles have an effective average particle size of less than about 1000 nm]; and

(b) freeze-drying the nanoparticulate dispersion to form a dry powder of aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns.

Please add the following new claims.

--59. The aerosol composition of claim 11, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

60. The aerosol composition of claim 11, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

61. The aerosol composition of claim 23, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

62. The aerosol composition of claim 23, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

63. The aerosol composition of claim 35, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

64. The aerosol composition of claim 35, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

65. The aerosol composition of claim 42, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

66. The aerosol composition of claim 42, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

67. The aerosol composition of claim 43, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

68. The aerosol composition of claim 43, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

69. The aerosol composition of claim 44, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

70. The aerosol composition of claim 44, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

71. The aerosol composition of claim 19, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

72. The aerosol composition of claim 19, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

73. The aerosol composition of claim 20, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

74. The aerosol composition of claim 20, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about

400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

75. The aerosol composition of claim 22, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

76. The aerosol composition of claim 22, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

77. The aerosol composition of claim 30, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

78. The aerosol composition of claim 30, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

79. The aerosol composition of claim 31, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

80. The aerosol composition of claim 31, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

81. The aerosol composition of claim 33, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

82. The aerosol composition of claim 33, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

83. The aerosol composition of claim 35, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies,

respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

84. The aerosol composition of claim 35, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

85. The aerosol composition of claim 35, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 10 microns.

86. The aerosol composition of claim 85, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 6 microns.

87. The aerosol composition of claim 35, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of less than about 2 microns.

88. The aerosol composition of claim 35, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 5 to about 100 μm.

89. The aerosol composition of claim 88, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 30 to about 60 μm.

90. The method of claim 40, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

91. The method of claim 40, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

92. The method of claim 40, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 10 microns.

93. The method of claim 92, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 6 microns.

94. The method of claim 40, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of less than about 2 microns.

95. The method of claim 40, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 5 to about 100 μm.

96. The method of claim 95, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 30 to about 60 μm.

97. The method of claim 42, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

98. The method of claim 42, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

99. The method of claim 42, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 10 microns.

100. The method of claim 99, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 6 microns.

101. The method of claim 42, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of less than about 2 microns.

102. The method of claim 42, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 5 to about 100 μm.

103. The method of claim 102, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 30 to about 60 μm.

104. The method of claim 43, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-

fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

105. The method of claim 43, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

106. The method of claim 43, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 10 microns.

107. The method of claim 106, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 6 microns.

108. The method of claim 43, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of less than about 2 microns.

109. The method of claim 43, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 5 to about 100 μm.

110. The method of claim 109, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 30 to about 60 μm.

111. The method of claim 44, wherein the drug is selected from the group consisting of proteins, peptides, bronchodilators, corticosteroids, elastase inhibitors, analgesics, anti-fungals, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease

therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, fungal infection therapies, and respiratory illness therapies associated with acquired immune deficiency syndrome, an oncology drug, an anti-emetic, an analgesic, and a cardiovascular agent.

112. The method of claim 44, wherein the nanoparticulate drug particles have an effective average particle size selected from the group consisting of less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 100 nm, and less than about 50 nm.

113. The method of claim 44, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 10 microns.

114. The method of claim 113, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 2 to about 6 microns.

115. The method of claim 44, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of less than about 2 microns.

116. The method of claim 44, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 5 to about 100 μm.

117. The method of claim 116, wherein the aggregates of the nanoparticulate drug particles have a mass median aerodynamic diameter of about 30 to about 60 μm.--